REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims.

Claim 56 has been amended to further clarify the invention. After entry of the amendment, claims 56 and 69-77 will be pending. Applicants submit the amendment does not raise any issues of new matter.

Applicants have added new claim 77. Applicants submit the new claim is supported throughout the specification, including at page 88, line 10 to page 89, line 21.

Objection to the Specification

The examiner objected to the specification because of the presence of a hyperlink. The specification was amended to remove the hyperlink. Applicants request withdrawal of the objection.

Written Description

Claim 56 was rejected under 35 U.S.C. § 112, first paragraph, as lacking written description. Applicants respectfully traverse this rejection.

Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claim 56 no longer refers to an immunogenic fragment. Applicants submit claim 56 as amended fully complies with the written description requirement. Withdrawal of the rejection is respectfully requested.

Enablement

Claims 56 and 69-76 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner has several bases for the rejection, including 1) the Examiner contends that there is no evidence that inhibition of stanniocalcin results in inhibition of angiogenesis, 2) the Examiner contends use of therapeutic antibodies to treat cancer is unpredictable, and 3) the Examiner contends pharmaceutical administration of antibodies to treat tumors is unpredictable. Applicants respectfully traverse this rejection.

Claim 56 as amended is drawn to a method of inhibiting angiogenesis in a mammal comprising administering to the mammal an effective amount of an antibody or antigen binding

fragment thereof that specifically binds and neutralizes a polypeptide comprising an amino acid sequence of SEQ ID NO:76. Claims 69-76 depend from claim 56.

The Office Action alleges the specification lacks critical guidance and objective evidence to predictably enable the practice of the invention as claimed. In particular, the Office Action alleges there is no evidence that inhibition of stanniocalcin results in inhibition of angiogenesis or that inhibiting stanniocalcin would predictably reduce tumor growth or metastasis. Applicants respectfully do not agree.

If the art is such that a particular model is recognized as correlating to a specific condition, then the model should be accepted as correlating unless the Examiner has evidence that the model does not correlate. *In re Brana*, 34 USPQ2d, 1436, 1441 (Fed. Cir. 1995); MPEP § 2164.02. Applicants have provided a working example showing upregulation of stanniocalcin precursor in endothelial cells undergoing tube formation. The endothelial cell model for tube formation is an art recognized model for angiogenesis. Davis et al., Exp. Cell. Res. 224:39-51 (1996). Applicants teach that stanniocalcin precursor expression is dramatically enhanced under tube-forming conditions (*see*, Example 19, page 142 of the specification and page 25, lines 20-26 of the specification). In contrast, lower levels of stanniocalcin precursor are expressed under conditions that do not foster tube formation. Applicants contend this data demonstrates a strong correlation between expression of stanniocalcin and tube-formation.

The Office Action has failed to provide any evidence that the endothelial model for tube formation does not correlate to angiogenesis. Moreover, the involvement of stanniocalcin in angiogenesis is confirmed by others. For example. Filvaroff *et al.* found that stanniocalcin 1 transgenic mice had significantly higher capillary density in organs and muscles compared with age-matched wildtype littermates (*see*, Filvaroff *et al.*, 2002, *Endocrinology* 143(9):3681-3690, page 3689, first column, third paragraph). Filvaroff *et al.* also found that stanniocalcin 1 transgenic mice showed a larger increase in vascularity after femoral ligation compared to wildtype littermates. Thus, overexpression of stanniocalcin 1 leads to an increase in vascularity *in vivo*. This data further supports involvement of stanniocalcin in angiogenesis.

The Office Action also alleges the use of therapeutic antibodies to treat cancer is unpredictable. Citing Gura, the Office Action alleges the fundamental problem in drug discovery for cancer is that the model systems are not predictive and that only 39 of the

thousands drugs shown to have activity in cell model or animal model have won approval from the FDA. Applicants respectfully do not agree.

As an initial matter, Applicants point out that the currently pending claims are directed to a method for inhibiting angiogenesis. The examiner's position concerning unpredictability of treatment of cancer does not take into account that a method of inhibiting angiogenesis as described by the specification is enabled, interalia, through the use of the art recognized model of angiogenesis, and has been confirmed by others.

Clinical approval is not a prerequisite for enablement (MPEP § 2164.05). Generally, the stage at which a biotechnological or pharmaceutical invention becomes useful is well before it is ready to be used in a clinical setting. *In re Brana*, 34 USPQ2d, 1436, 1443 (Fed. Cir. 1995). One of skill in the art would reasonably expect that an antibody that inhibits angiogenesis *in vitro* would inhibit angiogenesis *in vivo*. Antibodies that inhibit angiogenesis *in vitro* have been shown to inhibit angiogenesis *in vivo*. For example, anti-VEGF antibodies were known to inhibit angiogenesis both *in vitro* and *in vivo* (*see*, Presta *et al.*, 1997, *Cancer Res.*, 57:4593-4599) and have been approved by the FDA for treating cancer (see enclosed press release)).

Based on Applicants' teachings and the knowledge in the art related to inhibition of angiogenesis with antibody antagonists, one skilled in the art would expect that treatment with an agent that antagonizes stanniocalcin activity would inhibit angiogenesis. Applicants teach, for example, upregulation of stanniocalcin precursor in an art recognized model for angiogenesis and that neutralizing antibodies to stanniocalcin are useful as therapeutic molecules because they bind to stanniocalcin and thereby inhibit stanniocalcin activity (page 25, lines 17-19).

Applicants' teachings are also confirmed by other research in the field. For example, Filvaroff *et al.* found that overexpression of stanniocalcin 1 in mice leads to an increase in vascularity *in vivo*. Therefore, one skilled in the art would have had a reasonable expectation that neutralizing or antagonizing antibodies to stanniocalcin would be useful for inhibiting angiogenesis *in vivo* by preventing development of blood vessels during angiogenesis and/or vasculogenesis (page 12, lines 23-28 of the specification).

The Office Action also alleges the pharmaceutical administration of antibodies to treat tumors in mammals in unpredictable. Citing Jain, the Office Action alleges that delivery of antibodies to solid tumors, in particular, is unpredictable. Applicants respectfully do not agree.

Methods for enhancing antibody tumor penetration and biodistribution were known at the time of filing of the present application. Colcher et al., for example, describe methods to genetically engineer monoclonal Fv antibody fragments, including single chain antibody variable region (Fv), multi-valent single chain Fv constructs, multimeric noncovalent scFv, mulitmeric covalent scFv, and engineered multimeric scFv (*QJ Nucl. Med.*, 42:225-241, 1998). Colcher et al demonstrated that the smaller size of the Fv fragments allows for better tumor penetration and showed that antibody fragments accumulate in tumors. Using human adenocarcinomas expressing tumor-associated mucin, TAG-72, as a model for biodistribution studies in xenograft mice, blood ratios of anti-TAG-72 (CC49) scFv, Fab', $F(ab')_2$, and $(scFv)_2$ increased in tumor over time (Table II at page 234). The antibody fragments exhibited a much higher tumor:blood ratio at 24 and 48 hrs than IgG (Table IV at page 235). Eccles also discloses that antibody penetration into solid tumors can be improved by removing the constant (Fc) region and preparing monomeric or dimeric antibody fragments such as Fab, $F(ab')_2$, and scFV (*Breast Can. Res.*, 3:86-90, 2000 at page 87).

Applicants describe such antibody fragments and methods for making the fragments in the specification, for example, at page 41, lines 28 to page 42, line 18, page 42, line 26 to page 43, line 5, page 88, lines 5-7 and 11-14, and page 90, line 22 to page 91, line 22. In view of the teachings of the specification and the skill and knowledge in the art, as evidenced by Colcher et al. and Eccles, Applicants submit one of skill in the art would have reasonably expected that antibodies and fragments thereof that bind stanniocalcin would be useful for inhibiting tumor.

In view of the forgoing, Applicants submit the specification sufficiently teaches how to practice the claimed methods without undue experimentation. Withdrawal of the rejection is respectfully requested.

INTERVIEW REQUEST

Applicants request an interview with the Examiner and his supervisor to resolve any outstanding issues. Applicants request that the Examiner contact their representative upon receipt of these papers.

SUMMARY

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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